Sigma Agonists Modulate Functional Immune Activity of Rat Splenocytes.

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We have previously shown that *sigma* (σ1) receptors are present in rat spleen in strikingly high density, suggesting that σ receptors may provide a physiological mechanism for immune regulation. In the present study, we tested a variety of σ agonists for their ability to modulate the proliferative response of rat splenocytes to the mitogen concanavalin A (Con A). This *in vitro* functional activity correlates with general immune responsiveness of thymus-dependent (T) lymphocytes. Splenocytes from male Sprague-Dawley rats were isolated and incubated with drugs for 2hr at 37°C, then Con A (0.5 mg/ml) was added to the cells. The splenocytes were then incubated for 48hr at 37°C and ^{3}H-thymidine incorporation during the last 4-8hr of culture was used to determine their proliferation rates.

Sigma agonists suppressed the proliferation of rat spleen cells in a dose-dependent manner, with a rank order of potency (from most to least potent): rimcazole > spiperone > haloperidol > TCP > (-)butaclamol > PCP > (+) butaclamol > (+) pentazocine > DTG > (-)pentazocine $\geq$ (+)SKF 10,047 = (+)3-PPP > (-)SKF 10,047 > (-)3-PPP > BMY-14802.

The dose-response curves of these compounds showed two separate effects: 1) a low dose effect, usually producing <50% inhibition, which plateaued in most cases between drug concentrations of 10^{-6} and $3x10^{-5}$M, and 2) a high dose effect (>$3x10^{-5}$M) with a steep dose-response slope, producing complete suppression of ^{3}H-thymidine incorporation. The low dose effects were stereoselective for the *d*- or (+)-stereoisomers of pentazocine and 3-PPP, and the *l*- or (-)-stereoenantiomer of butaclamol. SKF 10,047 was less stereoselective. The high dose effects were not very stereoselective.

PCP and TCP were more potent than would be expected for actions *via* the haloperidol-labeled σ1 site that we have previously described in spleen. The putative σ antagonist BMY-14802 had a very shallow dose-response curve, resulting in <50% inhibition at all concentrations tested.

The observed pattern of drug potency suggests that these σ compounds modulate biological activities by at least two distinct mechanisms. The low dose drug effects are consistent with actions at stereoselective σ1 binding sites, while the high dose effects may represent either drug toxicity or actions at additional, lower affinity binding sites. Consistent with this notion, we have previously reported the existence of multiple binding sites for σ ligands in rat spleen (Soc. Neurosci. Abstracts 18: 456, #195.7, 1992).

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